Pestic. Sci. 1996, **48**, 175–178

The Pyrethrins and Related Compounds. Part XLI.* Structure–Activity Relationships in Non-ester Pyrethroids against Resistant Strains of Housefly (*Musca domestica* L.)

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(Received 15 January 1996; accepted 30 May 1996)

Abstract: A series of pyrethroids, related to NRDC 200 and etofenprox (MTI500) in which the central region is represented by a non-ester link, have been tested against one susceptible and two resistant strains (*kdr* and *super-kdr*) of houseflies (*Musca domestica* L.). A range of structural variations in the central region have been examined. Resistance factors mostly fell within narrow ranges for both resistant strains i.e. 10–50-fold resistance against *kdr* and 50–150-fold against *super-kdr*; thus no correlation of resistance with structural features was detectable for this region. Other changes examined were the substituent on the phenyl ring in the 'acid' component and the bridging group in the 'alcohol' component where small variations in response were observed. Examination of the effect of varying the 'alcohol' side chain was limited by lack of active analogues.

Key words: pyrethroids, non-ester, resistance, insecticide, housefly, *kdr*, *SAR*

1 INTRODUCTION

Since the introduction of photostable pyrethroids in the 1970s, the number of insect species which have developed resistance to them has increased steadily. Of the several types of resistance mechanism reported to date, that involving modification of the target site, referred to as the *kdr* mechanism, is one of the most important. Since the recognition of *kdr* in 1954, similar mechanisms have been invoked in many practical resistance situations. We are therefore systematically examining the whole of the pyrethroid molecule in a structure–activity relationship (SAR) study on the effect of structure on resistance. Houseflies are ideally suited for such a study because both *kdr* and *super-kdr* mechanisms have been fully characterised in substrains of housefly,[1] homogeneous specifically for each mechanism. The preceding papers in this series[2,3] examined the influence of structure in esters on levels of resistance against these strains.

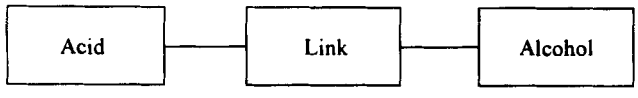

Fig. 1. General structure for pyrethroid.

Against the *kdr* strain, resistance factors (RF) were consistently in the range 20–60, implying no dependence of the level of resistance on the structure of the pyrethroid. However, against the *super-kdr* strain, the range was much larger (50–400) and a strong correlation between the nature of the alcohol component and RF was identified. Against both *kdr* and *super-kdr* strains, the nature of the acid component was shown to have no significant effect on RF.

The present study is an extension of the previous work and examines the influence of structural variation in the central region of the pyrethroid molecule on RF. In particular the ester group is replaced by sterically equivalent, non-ester alternatives, while the 'acid' and 'alcohol' components are also varied to some extent.

* Part XL. *Pestic. Sci.* **44** (1995) 277–81.

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The only other study of non-ester pyrethroids against resistant flies, reported by Pedersen,[4] was limited to analogues containing an ether linkage (e.g. etofenprox) and did not allow identification of any SARs.

2 EXPERIMENTAL

2.1 Chemicals

The compounds tested in the present study (except the three described below in Sections 2.1.4–2.1.6) were available from previously reported work.[5–9]

2.1.1 Synthesis

The [^{1}H] and [^{13}C]NMR spectra of synthesised compounds were determined on a JEOL GX-400 spectrometer (^{1}H frequency: 400 MHz, ^{13}C frequency: 100 MHz), using 32 or 64 K data points respectively. In all cases, samples were dissolved in deuterochloroform and tetramethylsilane was used as internal standard.

The term 'processed' in descriptions of synthesis implies extraction with diethyl ether (× 3), washing the organic layer with water (× 2), drying over magnesium sulfate and removing solvent using a rotary evaporator to yield a residue of product.

2.1.2 1-(3-(3-(1,3-Dioxolan-2-yl)phenyl)prop-1-enyl)-1-(4-ethoxyphenyl)cyclopropane

The Grignard reagent prepared from 2-(3-bromophenyl)-1,3-dioxolane (0·13 g) and magnesium (0·016 g) in tetrahydrofuran (5 ml) was added to a solution of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (0·02 g) and copper(I) chloride (0·006 g) in tetrahydrofuran (3 ml). After 10 min the mixture was cooled to −78°C and 1-(1-acetoxyprop-2-enyl)-1-(4-ethoxyphenyl)cyclopropane (0·1 g) in tetrahydrofuran (2 ml) added dropwise. After warming to room temperature over 1 h, the mixture was processed and chromatographed on a column of silica with diethyl ether + light petroleum distillate (1 + 8 by volume) to give the product (0·1 g, 80%), n_D 1·5538, [^{1}H]NMR peaks at 1·0 (m, 4H, 2 × CH_2), 1·4 (t, 3H, CH_3), 3·3 (d, 2H, CH_2), 4·0 (q, 2H, OCH_2), 4·1 (m, 4H, 2 × CH_2), 5·3 (m, 1H, CH =), 5·4 (d, 1H, CH =), 5·8 (s, 1H, CHO_2), 6·7–7·4 ppm (m, 8H, Ar).

2.1.3 1-(4-Ethoxyphenyl)-1-(3-(3-formylphenyl)prop-1-enyl)cyclopropane

15% Aqueous hydrochloric acid (2 ml) was added to a solution of 1-(3-(1,3-dioxolan-2-yl)phenyl)prop-1-enyl)1-(4-ethoxyphenyl)cyclopropane (0·2 g) in diethyl ether and stirred at room temperature for 30 min. Water was added and the mixture processed to give the product (0·16 g, 92%), n_D 1·5641, [^{1}H]NMR peaks at 0·9 (m, 4H, 2 × CH_2), 1·3 (t, 3H, CH_3), 3·3 (d, 2H, CH_2), 3·9 (q, 2H, OCH_2), 5·3 (m, 1H, CH=), 5·3 (m, 1H, CH=), 6·6–7·6 (m, 8H, Ar), 9·8 ppm (s, 1H, CHO).

2.1.4 1-(4-Ethoxyphenyl)-1-(3-(3-(α-hydroxybenzyl)phenyl)prop-1-enyl)cyclopropane (Compound no. 26)

1-(4-Ethoxyphenyl)-1-(3-(3-formylphenyl)prop-1-enyl) cyclopropane (0·16 g) in tetrahydrofuran (10 ml) was cooled to −78°C and a solution (1·0 M; 0·57 ml) of phenylmagnesium bromide in tetrahydrofuran added dropwise. After stirring for 30 min, the mixture was warmed to room temperature, processed and chromatographed from a column of silica using diethyl ether + light petroleum distillate (1 + 4 by volume) to give the product (0·1 g, 50%), n_D 1·5831, [^{1}H]NMR peaks at 0·87 (m, 2H, CH_2), 0·98 (m, 2H, CH_2), 1·38 (t, 3H, 7 Hz, CH_3), 3·25 (d, 2H, 6·5 Hz, CH_2), 3·98 (q, 2H, 7 Hz, OCH_2), 4·40 (1H, s, CHOH), 5·16 (1H, t, 7 Hz, CH=), 5·36 (1H, t, 15 Hz, CH=), 6·78–7·35 ppm (m, 13H, Ar) and [^{13}C]NMR peaks at 14·6 (2 × CH_2), 14·9 (CH), 27·0 (C_q), 38·5 (CH_2), 63·3 (CH_2), 76·2 (CH), 114·1 (2 × CH), 124·1 (CH), 126·5 (2 × CH), 126·6 (CH), 126·7 (CH), 127·4 (CH), 127·7 (CH), 128·4 (CH), 128·4 (2 × CH), 130·6 (2 × CH), 135·7 (C_q), 139·2 (CH), 139·7 (C_q), 141·2 (C_q), 143·8 (C_q), 157·3 ppm (C_q).

2.1.5 1-(3-Benzylbenzyloxymethyl)-1-(4-ethoxyphenyl)cyclopropane. Compound no. 27

A mixture of 1-(4-ethoxyphenyl)-1-hydroxymethylcyclopropane (0·1 g), 3-benzylbenzyl bromide (0·13 g), tetra-*n*-octylammonium bromide (0·05 g) and sodium hydroxide solution (500 g litre^{-1}; 5 ml) was stirred at 80°C for 3 h. On cooling, water (20 ml) was added, the mixture processed and the residue chromatographed from a column of silica with diethyl ether + light petroleum distillate (1 + 9 by volume) to give the product (0·07 g, 31%), n_D 1·5768, [^{1}H]NMR peaks at 0·79 (m, 4H, 2 × CH_2), 1·38 (t, 3H, 7 Hz, CH_3), 3·48 (s, 2H, CH_2), 3·92 (s, 2H, CH_2), 3·98 (q, 2H, 7 Hz, CH_2), 4·43 (s, 2H, CH_2), 7·04–7·28 ppm (m, 14H, Ar) and [^{13}C]NMR peaks at 11·5 (2 × CH_2), 14·9 (CH_3), 24·8 (C_q), 41·9 (CH_2), 63·3 (CH_2), 72·5 (CH_2), 77·7 (CH_2), 114·1 (2 × CH_2), 125·2 (CH), 126·0 (CH), 128·0 (CH), 128·0 (CH), 128·4 (CH), 128·4 (2 × CH), 129·0 (2 × CH), 129·8 (2 × CH), 135·5 (C_q), 138·8 (C_q), 139·1 (C_q), 141·1 (C_q), 157·3 ppm (C_q).

2.1.6 1-(3-Benzoylbenzyloxymethyl)-1-(4-ethoxyphenyl)cyclopropane. Compound no. 28

A solution of 1-(4-ethoxyphenyl)-1-hydroxymethylcyclopropane (0·1 g), 3-benzoylbenzylbromide (0·14 g) and tetra-*n*-octylammonium bromide (0·05 g) in sodium hydroxide (500 g litre^{-1}; 5 ml) was stirred at 80°C for 3 h. On cooling, water (10 ml) was added and the mixture processed. The residue was eluted from a column of silica with diethyl ether + light petroleum distillate (1 + 20 by volume) to give the product (0·11 g, 55%), n_D 1·5424, [^{1}H]NMR peaks at 0·81 (m, 4H, 2 × CH_2), 1·37 (t, 3H, 7 Hz, CH_3), 3·53 (s, 2H, CH_2), 3·97 (q, 2H, 7 Hz, CH_2), 4·51 (s, 2H, CH_2), 6·76–7·79 ppm

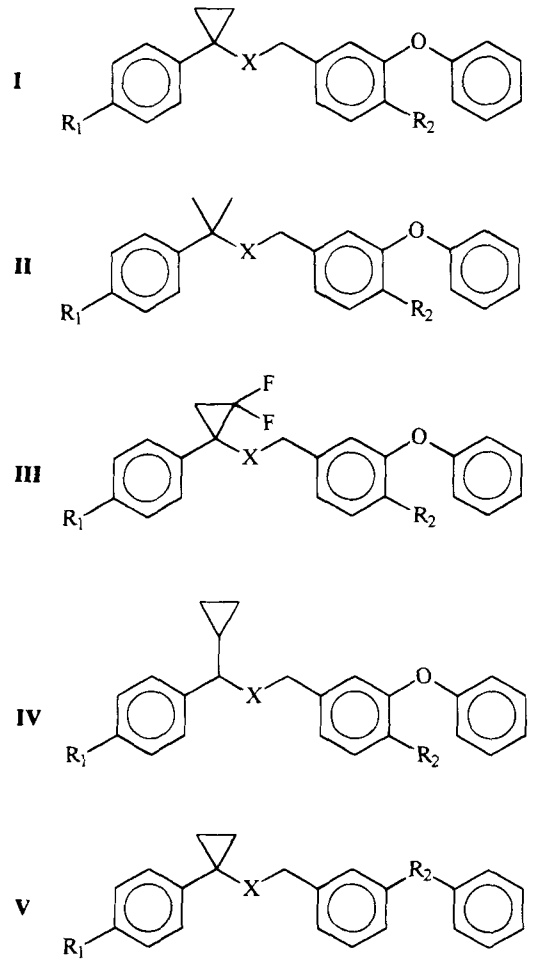

Fig. 2. Structures of compounds tested.

(m, 13H, Ar) and [^{13}C]NMR peaks at 11·6 (2 × CH_2), 14·9 (CH_3), 24·9 (C_q), 63·4 (CH_2), 72·2 (CH_2), 77·9 (CH_2), 114·1 (2 × CH), 128·3 (2 × CH), 128·4 (CH), 128·9 (CH), 129·2 (CH), 129·9 (2 × CH), 130·1 (2 × CH), 131·4 (CH), 132·5 (CH), 135·4 (C_q), 137·6 (C_q), 137·6 (C_q), 139·1 (C_q), 157·4 (C_q), 196·7 ppm (C_q).

2.2 Biological testing

Insecticidal activities against one strain of susceptible and two genetically pure strains of resistant adult *Musca domestica* L. (houseflies) each containing a single mechanism of resistance were assessed by topical application of measured drops of solutions of the compounds in acetone as described previously.[10] The results are presented in Table 1.

3 RESULTS AND DISCUSSION

In this study 28 compounds, incorporating five variations in the acid component, 14 variations in the central linkage and four variations in the alcohol component, have been investigated; the results are presented in Table 1. For clarity, LD_{50} values (μg per fly) are presented only for the susceptible strain, whilst, for the resistant strains, only resistance factors (RF) (obtained by dividing LD_{50} values for the resistant strains by the LD_{50} value of the susceptible strain) are given.

Against the *kdr* strain, RF values fall within a narrow range of 20 to 60 and no structure–activity relationships are discernible, thus indicating independence of levels of resistance and structural variations. The magnitude and range of RF values observed here are of the same order as those observed in the previous study against ester pyrethroids, thereby providing further support for the suggestion made there[2,3] i.e. that the resistance mechanism in *kdr* flies primarily attenuates the transmission of the excitatory signal generated on binding of the pyrethroid at the site of action. Against the *super-kdr* strain, RF values for all compounds based on 3-phenoxybenzyl alcohol (**5**, **7**, **10**, **12**, **14**, **18**, **19**, **21**, **23**, **24** and **25**) or its 4-fluoro derivative (**1–4**, **6**, **8**, **9**, **11**, **13**, **15–17**, **20** and **22**) also fall within a narrow range (50–150 fold) indicating that neither variations in the central linkage nor substituent effects in the acid component influence levels of resistance.

It is known[11] that 3-phenoxybenzyl- and the 4-fluoro-substituted analogues are the most effective 'alcoholic' groups in the non-ester pyrethroid series. Of the several other variations examined in the series, only three (compounds **26**, **27** and **28**) exhibited significant levels of insecticidal activity against both the susceptible and resistant strains. One (compound **27**) had a higher level of resistance than the 3-phenoxybenzyl analogues and another (compound **28**) a lower level. Further investigation was precluded by the lack of examples of non-ester pyrethroids with sufficient levels of activity (three other compounds made and tested). This was unfortunate in view of the fact that dependence of RF on structure was detected only in this region in our previous work with ester pyrethroid.[2,3] Overall, the results with these non-esters against resistant houseflies are closely parallel to those from the esters. There appears to be no contribution to variation in RF due to the nature of the central region, in contrast to the larger variations in RF when the side chain is changed.

ACKNOWLEDGEMENT

The authors thank Liz Cook, Mark Hedges, Simon Kingham, Andrew Peel, Sarah Perryman and Jean White for technical assistance and Norman Janes and Michael Elliott for advice and help in preparing the manuscript. This work was supported (in part) by the United Kingdom Ministry of Agriculture, Fisheries and Food and the British Technology Group Limited. IACR receives grant-aided support from the Biotechnology and Biological Sciences Research Council of the United Kingdom.

TABLE 1
Compounds Examined and Bioassay Results

Type[b]	Compound[a] Number		X	R_1	R_2	Strain of flies: Susceptible LD_{50} (μg per insect)	kdr RF1	Super-kdr RF2
I	1	(NRDC 199)	−CH=CH−	Cl	F	0·006	24	73
	2	(NRDC 200)		C_2H_5O	F	0·0039	23	110
	3			C_3H_7O	F	0·052	23	160
	4			F	F	0·021	31	100
	5			CHF_2O	H	0·0055	41	140
	6			CHF_2O	F	0·0068	40	100
	7		−CH=CF−	C_2H_5O	H	0·012	24	130
	8			C_2H_5O	F	0·017	13	100
	9		$-CH_2-CH_2-$	Cl	F	0·015	20	150
	10			C_2H_5O	H	0·039	22	130
	11		$-CH_2O-$	Cl	F	0·017	21	65
	12			C_2H_5O	H	0·017	38	150
	13			C_2H_5O	F	0·021	24	110
	14		$-CH_2CO-$	Cl	H	0·053	11	75
II	15		$-CH_2CH_2-$	Cl	F	0·078	27	72
	16	(MTI 800)		C_2H_5O	F	0·016	10	69
	17		$-CH_2O-$	Cl	F	0·013	28	130
	18	(MTI 500)		C_2H_5O	H	0·013	17	87
	19		$-CH_2CO-$	Cl	H	0·061	17	120
III	20		$-CH_2CH_2-$	C_2H_5O	F	0·012	13	150
	21		$-CH_2O-$	Cl	H	0·012	30	110
	22			Cl	F	0·0066	—	55
	23			C_2H_5O	H	0·018	—	41
IV	24		−CH=CH−	Cl	H	0·0043	20	95
	25		−CH=CF−	C_2H_5O	H	0·039	12	120
V	26		−CH=CH−	C_2H_5O	CHOH	0·15	43	130
	27		$-CH_2O-$	C_2H_5O	CH_2	0·07	63	230
	28			C_2H_5O	C=O	0·53	8·4	68

[a] −CH=CH− groups have E geometry and −CH=CF− have Z.
[b] See Fig. 2.

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